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Cost-effectiveness of ACE inhibitor therapy to prevent dialysis in nondiabetic nephropathy: influence of the ACE insertion/deletion polymorphism

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Introduction End-stage renal disease is associated with high health-care costs and low quality of life compared with chronic kidney disease. The renoprotective effectiveness of angiotensin-converting enzyme inhibitors (ACEi) is largely determined by the ACE insertion/deletion (I/D) polymorphism. We determined the cost-effectiveness of ACEi therapy in nondiabetic nephropathy for the ACE II/ID and for the ACE DD genotype separately. Furthermore, we considered a selective screen-and-treat strategy in which patients are prescribed alternative, more effective, therapy based on their ACE (I/D) polymorphism.

Methods Time-dependent Markov models were constructed; cohorts of 1000 patients were followed for 10 years. Data were mainly gathered from the Ramipril Efficacy In Nephropathy trial. Both univariate and probabilistic sensitivity analyses were performed.

Results ACEi therapy dominated placebo in both the ACE II/ID group (€15 826, and 0.091 quality-adjusted life years gained per patient) and the ACE DD group (€105 104 and 0.553 quality-adjusted life years gained). Sensitivity analyses showed 30.2% probability of ACEi being not cost-effective in the ACE II/ID group, against an almost 100% probability of cost-effectiveness in the ACE DD group. A selective screen-and-treat strategy should incorporate an alternative therapy for patients with the ACE II/ID genotype with an at least 9.1% increase in survival time compared with ACEi therapy to be cost-effective.

Introduction

Chronic kidney disease (CKD) is characterized by a decline in renal function, which may ultimately lead to end-stage renal disease (ESRD). Diabetes mellitus (DM) is one of the leading causes of CKD and subsequent ESRD. The European Renal Association-European Dialysis and Transplant Association reported that in Europe, prevalence of ESRD caused by DM type 1 or DM type 2 rose from 51.5 to 94.8 per million between 1992 and 2000 [1]. The prevalence of ESRD of nondiabetic origin rose from 455.8 to 607.2 per million in the same time period [1]. In The Netherlands, 3 095 patients suffered from ESRD of nondiabetic origin in 2008 [2].

Medical treatment modalities for ESRD patients include haemodialysis, peritoneal dialysis and renal transplantation;

Sensitivity analyses show that higher effectiveness and lower costs of the alternative therapy improve the cost-effectiveness of a screening strategy.

Conclusion ACEi therapy is a cost-saving treatment compared with placebo in nondiabetic nephropathy, irrespective of ACE (I/D) genotype. However, ACEi therapy saved more costs and more health gains were achieved in the ACE DD genotype than in the ACE II/ID genotype. An alternative treatment featuring a modest increase in effectiveness compared with ACEi therapy for patients with the ACE II/ID genotype can be incorporated in a cost-effective or even cost-saving screen-and-treat strategy. *Pharmacogenetics and Genomics* 19:695–703 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: angiotensin-converting enzyme inhibitors, chronic kidney failure, cost-effectiveness analysis, end-stage renal disease, genetic polymorphism

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with haemodialysis being the most and renal transplantation the least common modality [2]. Several studies have assessed the quality of life (QoL) of ESRD patients, invariably showing a considerably lower QoL in ESRD patients compared with CKD patients [3]. Costs of ESRD treatment modalities are high, with a share of the national expenditures in European countries ranging from 0.7% in the UK to 1.8% in Belgium (1.5% in France, 1.6% in Italy) [4]. Therefore, to delay or prevent the onset of ESRD is an important clinical goal.

ACEi efficacy and influence of the ACE (I/D) polymorphism

The renoprotective efficacy of angiotensin-converting enzyme inhibitors (ACEi) is undisputed. ACEi have been shown to delay the onset of ESRD in diabetic as well

as nondiabetic nephropathy [5,6]. However, individual differences in therapy response are large [7]. An important factor influencing ACEi efficacy is a polymorphism located in the ACE gene. This polymorphism was first described by Rigat *et al.* in 1990 [8] and is based on the presence (insertion, I) or absence (deletion, D) of a 287 base pair element in intron 16 of the ACE gene. A recent review presented an overview of the main studies evaluating the relationship between the ACE genotype and response to ACEi in nondiabetic renal disease [9]. The Ramipril Efficacy In Nephropathy (REIN) trial was the largest trial in terms of patient numbers and duration, and crucially was the only study that has used a hard endpoint, namely ESRD [5]. Patients with the ACE DD genotype showed increased susceptibility for ACEi therapy [10,11]. The finding that the ACE (I/D) polymorphism influences treatment efficacy in nondiabetic nephropathy has boosted research efforts for a treatment with increased effectiveness for patients with the ACE II/ID genotype. Such a treatment, incorporated in a selective screen-and-treat strategy, would have a high probability of being cost-effective or even cost saving, as the ACE II/ID genotype is common and the costs and disease burden associated with ESRD are high [12,13].

Study objectives

The importance of pharmacoeconomics for decision making is increasing in all fields of health-care, in particular regarding drug treatments. In that context it is useful to know the cost-effectiveness of ACEi therapy for the separate ACE (I/D) genotypes. Citing a checklist from our group on performing pharmacoeconomic analyses on pharmacogenetic screening interventions, an important starting point of such analyses is a comprehensive review of the evidence for the assumed association between genotype and phenotype [12]. No selective screen-and-treat strategy in nondiabetic nephropathy based on the ACE (I/D) polymorphism existed at the time, nor were studies found with conclusive evidence for such a strategy. Therefore, our first study objective was to understand the magnitude of difference in cost-effectiveness of ACEi therapy in association with the ACE genotype. In particular, we determined the cost-effectiveness of ACEi therapy versus non-renin-angiotensin system acting antihypertensive drugs in nondiabetic nephropathy separately for those with the ACE DD genotype and those with the ACE II/ID genotype. Our second study objective was to estimate cost-effectiveness of a selective screen-and-treat strategy involving an alternative treatment modality. By employing a threshold analysis, we determined the increase in effectiveness of an alternative treatment would require compared with the existing ACEi treatment to justify a screen-and-treat strategy, taking into account expected additional costs and health effects. This analysis should provide valuable information to researchers considering

new treatment modalities for nondiabetic nephropathy and to decision makers considering research budgets for such research.

Methods

Data

Data from the REIN trial were used for this economic analysis. The REIN trial was a randomized controlled trial in nondiabetic nephropathy aimed at determining the efficacy of the ACEi ramipril compared with placebo, at the same level of blood pressure control [5]. The REIN investigators found that the ACE (I/D) polymorphism was a strong predictor of ACEi efficacy; progression to ESRD was considerably and significantly reduced in ACEi-treated compared with placebo-treated patients with the ACE DD genotype (36% in placebo vs. 14% in ACEi), whereas a much smaller reduction was found in those with the ACE II/ID genotype (23% in placebo vs. 21% in ACEi) [10,11].

Models

Time-dependent Markov models were constructed with three health-states: CKD, ESRD and death. Cohorts of 1 000 patients entered the model and were followed for a time period of 10 years, and the health states were determined on monthly cycles. Given this short cycle time in the Markov model, no half-cycle correction was used. Patients were not allowed to recover from ESRD by reentering the CKD state.

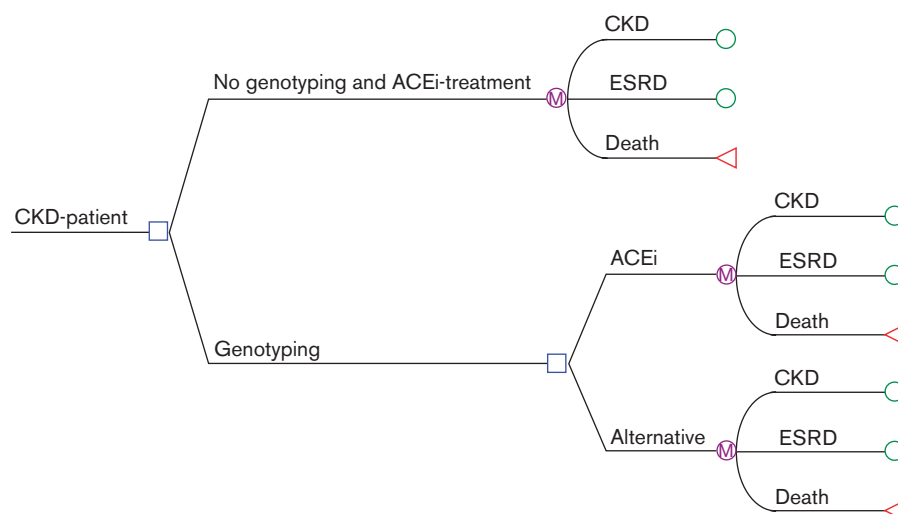
Cost-effectiveness analysis of ACEi therapy

For the first study objective, the cost-effectiveness of ACEi therapy was determined as compared with placebo therapy. Cost-effectiveness was determined for patients with the ACE II/ID and with the ACE DD genotype separately.

Threshold analysis for the selective screen-and-treat strategy

For our second study objective, we compared a selective screen-and-treat strategy with the absence of screening. For this goal, the Markov model was embedded in a decision-tree analytical framework (Fig. 1). In the nonscreening strategy, all patients received ACEi therapy. In the screening strategy, the ACE (I/D) genotype of all patients was screened; those with the ACE DD genotype received ACEi therapy, whereas those with the ACE II/ID genotype received an alternative renoprotective treatment. As no preferred treatment over ACEi for patients with ACE II/ID genotype currently exists, no prespecified effectiveness for this treatment was assumed. Instead, a threshold analysis was performed in which the effectiveness of the alternative treatment was varied. The increase in effectiveness of the alternative treatment compared with ACEi therapy needed for a screen-and-treat strategy to become cost-effective was determined.

Fig. 1



Decision tree model and Markov model; M represent the start of the Markov model, in which patients were followed for a time period of 10 years and allowed to move from one state to another per month. ACEi, angiotensin-converting enzyme inhibitors; CKD, chronic kidney disease; ESRD, end-stage renal disease.

Model parameters

Five parametric survival distributions (Weibull, exponential, lognormal, loglogistic and Gaussian) were fitted on the REIN data by maximizing the likelihood ratio; the Akaike information criterion (lower value indicates better fit) was calculated for each distribution [14]. The effectiveness of ACEi compared with placebo in our model was based on the parameters of the best-fit distribution.

Mortality rates of patients with CKD were calculated using data from the REIN and a similar trial in nondiabetic nephropathy, REIN-2 [15]. In these trials, nine deaths occurred over a cumulative follow-up of 1700 patient-years, resulting in an annual mortality rate of 0.53% per year [5,15]. Patients in the REIN trial were followed until ESRD development or death [5]; therefore no data on ESRD mortality were available. Mortality rates of ESRD patients were instead derived from the Dutch End-Stage Renal Disease Registry (RENINE), using data from 1998 to 2008 [2]. No differences in mortality rates between the ACE polymorphisms or treatment arms were assumed.

ACE (I/D) polymorphism prevalences were derived from several clinical trials in nondiabetic nephropathy [10,11,16–20], all described in a systematic review by Ruggenenti *et al.* [9]. QoL estimates were obtained by examining a recently published systematic review [3], in which one study was reported with QoL estimates for CKD and ESRD based on community preferences, using the Health Utilities Index-3 [21]. In economic evaluations, community or societal preferences are preferred over patient preferences [22].

A third-party payer perspective for the cost estimates was adopted. Costs of ESRD were based on a weighted average of Dutch cost estimates for active haemodialyses, passive haemodialyses and peritoneal dialysis, adjusted for inflation to 2008 values [23]. Costs of ramipril treatment were based on 2008 Dutch prices [24], including 6% value-added tax and a 3-monthly pharmacists' prescription fee of €6.10. In the REIN trial, ACEi therapy was compared with placebo treatment; both treatment arms received similar additional blood pressure lowering drugs and health-care services [5]. Associated health-care costs were equal in both groups and therefore not included in our analysis. The costs of an alternative treatment modality in the screening strategy were based on Dutch prices for the new renin inhibitor aliskiren [24], to reflect costs for a new treatment modality; these costs were varied in sensitivity analyses. The price of a genetic screening test for the ACE (I/D) polymorphism was based on polymerase chain reaction and included staff costs [25]. Costs and health effects were discounted at 3% per annum, following recommendations by Gold *et al.* [22] and Drummond *et al.* [26]. An overview of all parameters is shown in Table 1.

Sensitivity analysis

Univariate and probabilistic sensitivity analyses were performed for both the cost-effectiveness analysis and the threshold analysis. In the univariate sensitivity analyses, all model parameters were varied by 25% to determine the main cost and effect drivers in our model. Discount rates were varied based on Dutch guidelines for pharmacoeconomic research recommending differential discounting for costs and health effects, at 4 and 1.5%,

Table 1 Parameters used in the analyses

Variable	Baseline value	Univariate sensitivity range	Probabilistic sensitivity distribution	Reference
Genotype prevalences				
ACE DD prevalence	32.87%	24.65–41.08%	Beta	[10,11,16–20]
Costs				
Dialysis (per year)	€72 354	€54 265–€90 443	Triangular	[23]
ACEi therapy (per month)	€3.03	€2.27–€3.79	Triangular	[24]
Alternative therapy (per month)	€23.67	€17.75–€29.59	Triangular	[24]
Genetic screening test	€50.00	€37.50–€62.50	Triangular	[25]
Health effects				
QoL chronic kidney disease	0.67	0.50–0.84	Beta	[21]
QoL dialysis	0.54	0.41–0.68	Beta	[21]
Annual mortality rate – CKD	0.53%	0.40%–0.66%	Poisson	[5,15]
Annual mortality rate – ESRD	9.95%	7.46%–12.44%	Poisson	[1]
ACEi effectiveness in ACE II/ID (days) ^a	15.3	11.5–19.1	Bootstrapping	[11]
ACEi effectiveness in ACE DD (days) ^a	106.1	79.6–132.6	Bootstrapping	[11]
Effectiveness of alternative treatment in screening strategy (days) ^b		Varied in the threshold analysis		

Ranges for univariate sensitivity analysis were $\pm 25\%$ for all parameters.

ACEi, angiotensin-converting enzyme inhibitor; CKD, chronic kidney disease; ESRD, end-stage renal disease; QoL, quality of life.

^aEffectiveness of ACEi therapy was defined as prolongation of median time to ESRD compared with placebo.

^bEffectiveness of the alternative treatment was defined as increase in effectiveness compared with ACEi therapy.

Table 2 Cost-effectiveness at baseline and probabilistic sensitivity analysis

Cost-effectiveness of ACEi therapy								
	ACEi therapy		Placebo		Cost-effectiveness of ACEi therapy			
	Costs	QALYs	Costs	QALYs	Δ Costs	Δ QALYs	Costs/QALY	Probability of cost-effectiveness (%) ^a
All patients	€115 826	5.130	€160 789	4.887	€ – 45 168	0.242	Dominance	97.6
ACE II/ID genotype group	€125 786	5.078	€141 612	4.988	€ – 15 826	0.091	Dominance	69.8
ACE DD genotype group	€94 860	5.235	€199 963	4.682	€ – 105 104	0.553	Dominance	99.8
Threshold analysis for the selective screen-and-treat strategy								
	Screening strategy		Nonscreening strategy		Cost-effectiveness of screening			
	Costs	QALYs	Costs	QALYs	Δ Costs	Δ QALYs	Costs/QALY	Probability of cost-effectiveness (%) ^a
No increase in effectiveness	€ – 44 221	0.243	€ – 45 198	0.243	€977	0.000	Dominated	0
9.1% Increase in effectiveness ^b	€ – 45 102	0.248	€ – 45 198	0.243	€96	0.005	€19 477	72.3
25% Increase in effectiveness ^b	€ – 46 606	0.256	€ – 45 198	0.243	€ – 1 408	0.013	Dominance	89.8

The term 'dominance' denotes that a strategy saves costs as well as QALYs compared with its comparator strategy (which is then said to be 'dominated').

ACEi, angiotensin-converting enzyme inhibitor; QALY, quality-adjusted life year.

^aThe probability of cost-effectiveness was determined in the probabilistic sensitivity analysis.

^bEffectiveness of the alternative treatment was defined as increase in effectiveness compared with ACEi therapy, which was defined as prolongation of median time to ESRD compared with placebo.

respectively [27,28]. Results of the univariate sensitivity analysis are presented in a tornado diagram [29]. In the probabilistic sensitivity analyses, triangular distributions were used for all cost parameters; beta distributions for ACE (I/D) genotype prevalences and QoL estimates; and Poisson distributions for mortality probabilities. Variation in ACEi effectiveness was captured by nonparametric bootstrapping, in which a random sample of the same size as the original data is drawn with replacement. This procedure is performed a large number of times. Bootstrapping is used to estimate the true distribution of a sample regardless of the distribution of the original data [29]. The probabilistic sensitivity analysis was run 10 000 times.

Statistics

Fitting and bootstrapping of the REIN data were performed in the statistical package R, version 2.5.1 [30]. The models and sensitivity analyses were constructed in Microsoft Office Excel 2003.

Results

Five parametric distributions (Weibull, exponential, lognormal, loglogistic and Gaussian) were fitted on the REIN data. Akaike information criterion values and visual assessment showed that the lognormal distribution provided the best fit for both genotype groups and both treatment arms. This distribution was therefore selected for use in the Markov model.

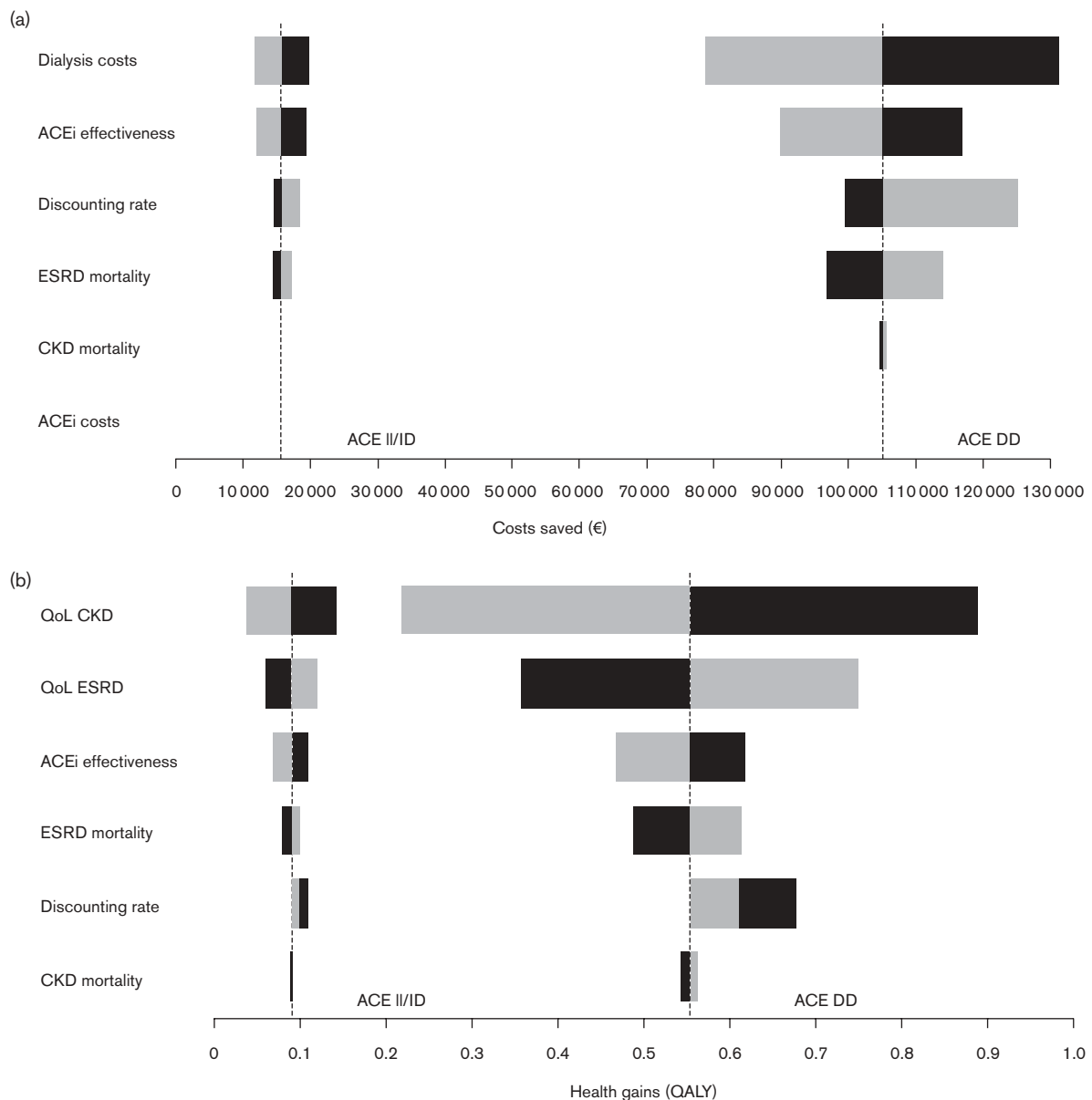
Cost-effectiveness of ACEi therapy

In the baseline analysis (Table 2), ACEi therapy dominated placebo in both genotype groups, that is, resulted in clinical benefits as well as cost-savings. In the 10-year time frame, cost savings for a patient with the ACE II/ID genotype was €15 826 and €105 104 for a patient with the ACE DD genotype. Overall, ACEi therapy resulted in cost savings of €45 198. Quality-adjusted life years (QALYs) gained per patient were

0.091 for a patient with the ACE II/ID genotype and 0.553 for ACE DD. Overall, ACEi therapy gained 0.243 QALYs per patient in the 10-year time frame.

Univariate sensitivity analysis showed that dialysis costs and ACEi effectiveness had the largest influence on the cost savings of ACEi therapy in both genotype groups (Fig. 2a). The main drivers of health gains were QoL of CKD and ESRD patients, followed by ACEi effectiveness

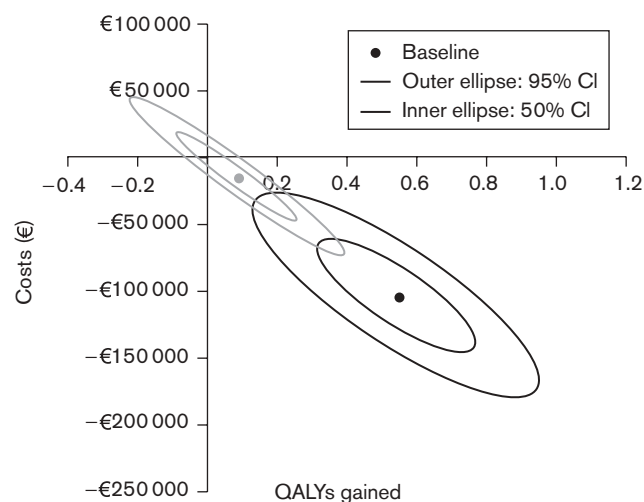
Fig. 2



(a and b) Univariate sensitivity analysis for net cost savings (a) and health gains (b) of angiotensin-converting enzyme inhibitors (ACEi) therapy; the dashed line represents the baseline analysis. Black bars denote influence of the high end of the sensitivity range and grey bars denote influence of the low end of the sensitivity range. Discounting rate was varied to 0% for both costs and health gains on the low end and 4 and 1.5% on the high end for costs and health gains, respectively. CKD, chronic kidney disease; ESRD, end-stage renal disease; QALY, quality-adjusted life year; QoL, quality of life.

(Fig. 2b). Probabilistic sensitivity analysis (Fig. 3; Table 2) showed that in the ACE II/ID genotype, ACEi therapy has a 30.2% probability of resulting in an unfavourable outcome (no health benefits or cost-effectiveness of more than €20 000 /QALY). In the ACE DD genotype,

Fig. 3



Cost-effectiveness plane for angiotensin-converting enzyme inhibitors (ACEi) treatment in nondiabetic nephropathy for patients with the ACE II/ID genotype (grey ellipse) and ACE DD genotype (black ellipse); baseline analysis; 95 and 50% confidence intervals (CIs) are shown. QALYs, quality-adjusted life years.

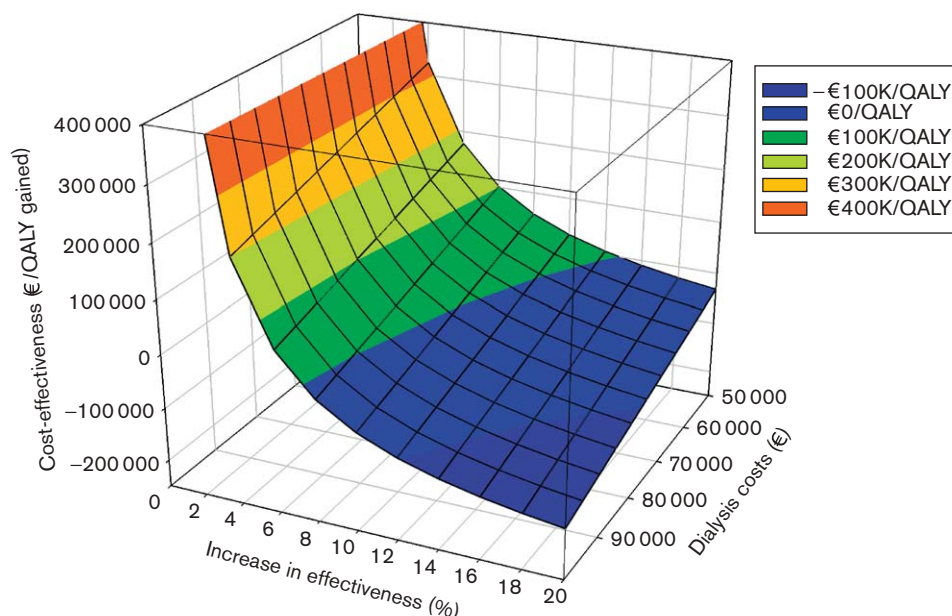
however, there was only a 0.2% probability of an unfavourable cost-effectiveness outcome.

Threshold analysis for the selective screen-and-treat strategy

A selective screen-and-treat strategy was based on the decision-tree analytical framework and Markov model (Fig. 1). The effectiveness of the alternative treatment for ACE II/ID patients in the screening arm of this strategy was varied in a threshold analysis. Results are presented in Table 2. This analysis showed that an alternative treatment should increase effectiveness compared with ACEi therapy by 9.1% for a screening strategy to be cost-effective compared with a nonscreening strategy. Probabilistic sensitivity analysis showed that the chance of cost-effectiveness under this assumption is 72.3%. With an increase in effectiveness of the alternative treatment of 25%, a screening strategy would save €1 408 and 0.013 QALY per patient, thus resulting in a dominating strategy compared with nonscreening. The chance of cost-effectiveness under this assumption was 89.8%. When no increase in effectiveness of the alternative treatment was assumed, a screening strategy would generate extra costs and no health gains, thus causing the screening strategy to be dominated by the nonscreening strategy.

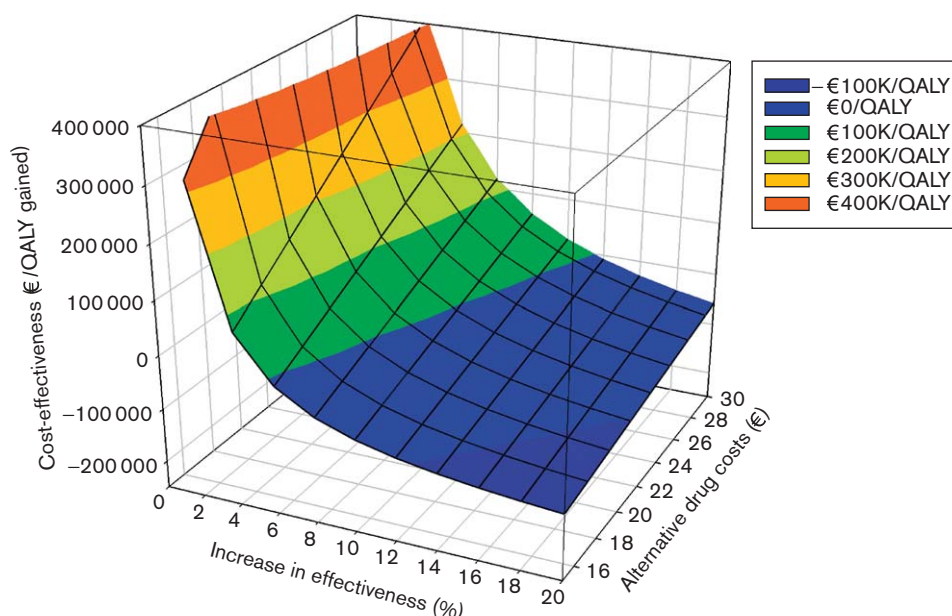
Univariate sensitivity analyses showed that the costs of dialysis and of the alternative therapy were the most influential factors on the variability of the cost-effectiveness

Fig. 4



Two-way sensitivity analysis on the cost-effectiveness of a selective screen-and-treat strategy; dialysis costs and effectiveness of the alternative treatment modality. Negative cost-effectiveness values denote cost-savings and health gains. QALY, quality-adjusted life year.

Fig. 5



Two-way sensitivity analysis on the cost-effectiveness of a selective screen-and-treat strategy; costs and effectiveness of the alternative treatment modality. Negative cost-effectiveness values denote cost savings and health gains. QALY, quality-adjusted life year.

estimates. Two-way analyses were performed for these two variables and the effectiveness of the alternative treatment (Figs 4 and 5). Lower costs of dialysis and higher costs of the alternative treatment decreases the cost-effectiveness of a screening strategy.

Discussion

This study showed that ACEi therapy is a cost-saving treatment modality to prevent ESRD in nondiabetic nephropathy irrespective of ACE genotype, based on the Caucasian population of the REIN trial. However, although ACEi is cost saving for all patients, there are considerable differences in cost-effectiveness in the different ACE (I/D) genotypes. ACEi therapy, compared with non-renin-angiotensin system acting antihypertensive drugs, resulted in more costs-savings and more health gains in the ACE DD group than in the ACE II/ID group. In addition, in the ACE II/ID genotype, there was a 30.2% probability of ACEi therapy resulting in an unfavourable cost-effectiveness outcome, while the chance of ACEi therapy being cost-effective or even cost saving in the ACE DD genotype was almost 100%. Although separate analyses for the different polymorphisms have not been performed before, the finding that ACEi therapy is a cost-effective treatment in nondiabetic nephropathy has been reported in other studies. Van Hout *et al.* [31] analyzed ACEi cost-effectiveness based on the ACE Inhibition in the Progressive Renal Insufficiency trial, and found ACEi therapy to save \$28 014 per patient, using a time frame of 10 years (in

1996 US\$, equivalent to €30 272 in 2008 price levels). Ruggenenti *et al.* [32] performed a cost-effectiveness analysis based on the REIN trial and found ACEi therapy to save between \$16 605 and \$23 894 per lifetime (in 2000 US\$, equivalent to €20 887 and €30 056 in 2008 price levels). Schädlich *et al.* [33] reported cost savings between 76 700 and 81 900 Deutschmarks per patient-year of chronic dialysis avoided, using a time frame of 1–3 years (in 1999 Deutschmarks, equivalent to €51 168 and €54 637 in 2008 price levels). Our model demonstrated cost savings of ACEi therapy compared with placebo of €45 198 per patient using a 10-year time frame (ACE II/ID and ACE DD combined). Overall, cost savings per patient-year of chronic dialysis avoided were €60 597. The larger cost savings in our study compared with previous studies can be explained by lower discounting rates and higher costs of dialysis assumed in our model compared with the other studies.

The main limitation of this study is the assumption of an association between the ACE (I/D) polymorphism and ACEi therapy response, which is still disputed. In fact, several studies reported that the D allele is associated with ACEi therapy resistance [16,19], contrary to our model assumptions. The trial used for our analyses was the only trial evaluating a hard endpoint, namely ESRD. A recent analysis in one of the contradicting trials [19] showed that the preintervention rate of renal function loss (measured as creatinine clearance) was significantly higher in the ACE DD group compared with the other genotype groups [34]. Taking this preintervention rate

into account, ACEi therapy did in fact benefit patients with the ACE DD genotype, but not those with ACE II/ID genotype [34]. Therefore, although the REIN trial was the largest trial on the subject, other studies seem to confirm the findings. However, environmental factors should also be considered when determining the association between ACE genotype and ACEi response. ACEi therapy response is also dependent on sodium status, with more effective response on low sodium excretion in the ACE DD genotype [17].

We employed a third-party perspective for our cost estimates as opposed to a societal perspective. Although many guidelines recommend adoption of a societal perspective, for a first assessment of the cost-effectiveness of genetic screening interventions, there are limitations in performing this in our case because of a lack of data in developmental stages and data being based on efficacy as opposed to real-life effectiveness [12]. In addition, the third-party focus is often of prime interest to payer decision makers. However, for full understanding of the economic impact, indirect costs should be considered before final decisions on implementations of screening strategies are made [12].

The models and parameters used in this economic analysis have been kept as relevant and transparent as possible. However, as in all economic analyses, several assumptions and estimates were made. Sensitivity analyses showed that mortality rates had a minor influence of the cost-effectiveness of the treatment modalities. Mortality rates in CKD were estimated from data obtained from the REIN and REIN-2 study combined. Mortality rates in ESRD were assumed to be similar in both ACE genotype groups. There is evidence that mortality is higher in dialysis patients with the ACE DD genotype [35]; however no information on ACEi therapy versus other antihypertensive drugs was reported. The most influential factor in sensitivity analyses was the cost of dialysis. When higher dialysis costs were assumed, ACEi therapy became more cost-effective in both ACE genotypes. Cost-effectiveness of the selective screen-and-treat strategy also increased with higher dialysis costs, but was also dependent on the assumed effectiveness and costs of the alternative treatment; these factors should therefore be taken into account when developing an alternative treatment to be employed in a selective screen-and-treat strategy.

Conclusion

The ACE (I/D) polymorphism is a large determinant of response to ACEi therapy not only in terms of health outcomes but also of cost-effectiveness. This study showed that ACEi therapy compared with placebo both reduces costs and improves QALYs more in the ACE DD group than in the ACE II/ID group, although

ACEi treatment remains cost saving in both genotypes. A selective screen-and-treat strategy based on a treatment modality, which produces a modest increase in effectiveness in patients with the ACE II/ID genotype, can result in large cost savings and clinical benefits. Unfortunately, clinical evidence for such a selective screen-and-treat strategy has been scarce and no such strategy has yet been implemented in clinical practice. Before this, ACEi therapy should be given to nondiabetic nephropathy patients irrespective of ACE genotype. Still, the large potential cost savings and clinical benefits associated with a selective screen-and-treat strategy should ensure that studies and trials in this field remain appealing for both researchers and decision makers.

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References

- 1 Van Dijk PC, Jager KJ, Stengel B, Gronhagen-Riska C, Feest TG, Briggs JD. Renal replacement therapy for diabetic end-stage renal disease: data from 10 registries in Europe (1991-2000). *Kidney Int* 2005; **67**:1489-1499.
- 2 Dutch End-Stage Renal Disease Registry (RENINE). 2009.
- 3 Dale PL, Hutton J, Elgazzar H. Utility of health states in chronic kidney disease: a structured review of the literature. *Curr Med Res Opin* 2008; **24**:193-206.
- 4 Peeters P, Rublee D, Just PM, Joseph A. Analysis and interpretation of cost data in dialysis: review of Western European literature. *Health Policy* 2000; **54**:209-227.
- 5 The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; **349**:1857-1863.
- 6 Ruggerenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004; **351**:1941-1951.
- 7 Heeg JE, de Jong PE, van der Hem GK, de ZD. Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int* 1989; **36**:272-279.
- 8 Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene

- accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990; **86**:1343–1346.
- 9 Ruggenenti P, Bettinaglio P, Pinares F, Remuzzi G. Angiotensin converting enzyme insertion/deletion polymorphism and renoprotection in diabetic and nondiabetic nephropathies. *Clin J Am Soc Nephrol* 2008; **3**:1511–1525.
 - 10 Ruggenenti P, Perna A, Zoccali C, Gherardi G, Benini R, Testa A, *et al.* Chronic proteinuric nephropathies. II. Outcomes and response to treatment in a prospective cohort of 352 patients: differences between women and men in relation to the ACE gene polymorphism. Gruppo Italiano di Studi Epidemiologici in Nefrologia (Gisen). *J Am Soc Nephrol* 2000; **11**:88–96.
 - 11 Perna A, Ruggenenti P, Testa A, Spoto B, Benini R, Misefari V, *et al.* ACE genotype and ACE inhibitors induced renoprotection in chronic proteinuric nephropathies. *Kidney Int* 2000; **57**:274–281.
 - 12 Vegter S, Boersma C, Rozenbaum M, Wilffert B, Navis G, Postma MJ. Pharmacoeconomic evaluations of pharmacogenetic and genomic screening programmes: a systematic review on content and adherence to guidelines. *Pharmacoeconomics* 2008; **26**:569–587.
 - 13 Flowers CR, Veenstra D. The role of cost-effectiveness analysis in the era of pharmacogenomics. *Pharmacoeconomics* 2004; **22**:481–493.
 - 14 Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15**:361–387.
 - 15 Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-lordache B, Turturro M, *et al.* Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365**:939–946.
 - 16 Haas M, Yilmaz N, Schmidt A, Neyer U, Arneitz K, Stummvoll HK, *et al.* Angiotensin-converting enzyme gene polymorphism determines the antiproteinuric and systemic hemodynamic effect of enalapril in patients with proteinuric renal disease. Austrian Study Group of the Effects of Enalapril Treatment in Proteinuric Renal Disease. *Kidney Blood Press Res* 1998; **21**:66–69.
 - 17 Van der Kleij FG, Schmidt A, Navis GJ, Haas M, Yilmaz N, de Jong PE, *et al.* Angiotensin converting enzyme insertion/deletion polymorphism and short-term renal response to ACE inhibition: role of sodium status. *Kidney Int Suppl* 1997; **63**:S23–S26.
 - 18 Van der Kleij FG, Navis GJ, Gansevoort RT, Heeg JE, Scheffer H, de ZD, *et al.* ACE polymorphism does not determine short-term renal response to ACE-inhibition in proteinuric patients. *Nephrol Dial Transplant* 1997; **12** (Suppl 2):42–46.
 - 19 Van Essen GG, Rensma PL, de ZD, Sluiter WJ, Scheffer H, Apperloo AJ, *et al.* Association between angiotensin-converting-enzyme gene polymorphism and failure of renoprotective therapy. *Lancet* 1996; **347**:94–95.
 - 20 Yoshida H, Mitarai T, Kawamura T, Kitajima T, Miyazaki Y, Nagasawa R, *et al.* Role of the deletion of polymorphism of the angiotensin converting enzyme gene in the progression and therapeutic responsiveness of IgA nephropathy. *J Clin Invest* 1995; **96**:2162–2169.
 - 21 Gorodetskaya I, Zenios S, McCulloch CE, Bostrom A, Hsu CY, Bindman AB, *et al.* Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney Int* 2005; **68**:2801–2808.
 - 22 Gold M, Siegel J, Russell L. *Cost-effectiveness in health and medicine*. New York: Oxford University Press; 1996.
 - 23 De Wit GA, Ramsteijn PG, de Charro FT. Economic evaluation of end stage renal disease treatment. *Health Policy* 1998; **44**:215–232.
 - 24 Dutch drug prices [in Dutch]. Available at: <http://www.medicijnkosten.nl>. Accessed August 2008.
 - 25 Costa-Scharplatz M, van Asselt AD, Bachmann LM, Kessels AG, Severens JL. Cost-effectiveness of pharmacogenetic testing to predict treatment response to angiotensin-converting enzyme inhibitor. *Pharmacogenet Genomics* 2007; **17**:359–368.
 - 26 Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005.
 - 27 Brouwer WB, Niessen LW, Postma MJ, Rutten FF. Need for differential discounting of costs and health effects in cost effectiveness analyses. *BMJ* 2005; **331**:446–448.
 - 28 Oostenbrink JB, Bouwmans CA, Koopmanschap MA, Rutten FF. *Guideline for costing research, methods and standardized prices for economic evaluations in health care*. Diemen, The Netherlands: Health Care Insurance Board; 2004.
 - 29 Berger ML, Bingefors K, Hedblom EC, Pashos CL, Torrance GW. *Health care costs, quality, and outcomes – ISPOR book of terms*. Lawrenceville, NJ: International Society of Pharmacoeconomics and Outcomes Research (ISPOR); 2003.
 - 30 Foundation for Statistical Computing. R: A language and environment for statistical computing. 2007. Vienna, Austria. Ref Type: Computer Program
 - 31 Van Hout BA, Simeon GP, McDonnell J, Mann JF. Economic evaluation of benazepril in chronic renal insufficiency. *Kidney Int Suppl* 1997; **63**:S159–S162.
 - 32 Ruggenenti P, Pagano E, Tammuzzo L, Benini R, Garattini L, Remuzzi G. Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies. *Kidney Int* 2001; **59**:286–294.
 - 33 Schädlich PK, Brecht JG, Brunetti M, Pagano E, Rangoonwala B, Huppertz E. Cost effectiveness of ramipril in patients with non-diabetic nephropathy and hypertension: economic evaluation of Ramipril Efficacy in Nephropathy (REIN) Study for Germany from the perspective of statutory health insurance. *Pharmacoeconomics* 2001; **19**:497–512.
 - 34 Lely AT, van der Kleij FG, Kistemaker TJ, Apperloo AJ, de Jong PE, de ZD, *et al.* Impact of the preintervention rate of renal function decline on outcome of renoprotective intervention. *Clin J Am Soc Nephrol* 2008; **3**:54–60.
 - 35 Van der Sman-de Beer F, Verhagen C, Rombach SM, Boersma P, van Manen JG, Korevaar JC, *et al.* ACE I/D polymorphism is associated with mortality in a cohort study of patients starting with dialysis. *Kidney Int* 2005; **68**:2237–2243.
 - 36 Brenchley PE, Lindholm B, Dekker FW, Navis G. Translating knowledge of the human genome into clinical practice in nephrology dialysis and transplantation: the renal genome network (ReGeNet). *Nephrol Dial Transplant* 2006; **21**:2681–2683.